REMARKS

Claims 1-24 are currently pending in this application. Claims 7-12 and 19-24 have been withdrawn from consideration. By this amendment, claims 1, 4, 6, 13, 16, and 18 have been amended, claims 2 and 14, have been canceled, and claims 25-42 have been newly added. Examiner Li's comments in the December 29, 2005 Office Action have been carefully considered and reconsideration of this application in view of the current amendments and following remarks is respectfully requested.

Support for the amendments presented herein can be found throughout in the subject application. For example, applicants disclose in paragraph 7 on page 1 that "another common feature of heart failure is the occurrence of cardiac arrhythmias. Ventricular arrhythmias in the heart can be rapidly fatal, a phenomenon referred to as sudden cardiac death (SCD). SCD is associated with common cardiac diseases, most notably heart failure, in which approximately 50% of patients die from fatal cardiac arrhythmias. However, fatal ventricular arrhythmias can also occur in young, otherwise healthy individuals without known structural heart disease." In paragraph 8 of page 1, applicants also disclose that "CPVT is predominantly inherited in an autosomal-dominant fashion. Affected individuals present during childhood or adolescence with repetitive exercise-induced syncopal events with 30-50% mortality by age 30 (Fisher et al., 1999; Swan et al.,1999). Linkage studies and direct sequencing have identified mutations in the human RyR2 gene (hRyR2) on chromosome 1q42-q43 in individuals with CPVT (Laitinen et al., 2001; Priori et al., 2001; Swan et al., 1999). Importantly, individuals with CPVT have ventricular arrhythmias when subjected to exercise testing, but they do not have these arrhythmias at rest." Applicants further disclose in paragraph 60 on page 7 that "a "subject" may be any animal, such as a mammal or a bird, including, without limitation, a cow, a horse, a sheep, a pig, a dog, a cat, a rodent such as a mouse or rat, a turkey, a chicken and a primate. In the preferred embodiment, the subject is a human being" and in paragraph 105 on page 10 that "human cardiac tissue was fixed in 10% neutral buffered formalin, and embedded in paraffin." Thus, the subject application provides support for the amendments made to claims 1, 4, 13, and 16, as well as the newly added claims that address a human subject.

Applicants disclose in paragraph 227 on page 22 that "it has previously been shown that FKBP12.6 cannot bind to PKA-phosphorylated RyR2 (Marx et al., 2001; Marx et al., 2000)" and in the following paragraph state that "in contrast to wild-type FKBP12.6, FKBP12.6-D37S was capable of binding to RyR2 channels isolated from exercised FKBP12.6$^{-/-}$ mouse hearts (FIG. 12C) and restored normal channel function (FIG. 12D)." Applicants further disclose in paragraph 256 on page 24 that "JTV-519 enables FKBP12.6 to bind to PKA-phosphorylated RyR2 (partial binding at 100 nM, complete binding at 1000 nM)." Thus, the subject application provides support for the amendments made to claim 1 and 13, as well as the newly added claims.

Support for the new claims presented herein can be found throughout the specification of the application. For example, applicants disclose in paragraph 59 on page 7 that ""administering" means delivering in a manner which is effected or performed using any of the various methods and delivery systems known to those skilled in the art. Administering can be performed, for example, topically, intravenously, pericardially, orally, via implant, transmucosally, transdermally, intramuscularly, subcutaneously, intraperitoneally, intrathecally, intralymphatically, intralesionally, or epidurally." In paragraph 256 of page 24 (as stated above), applicants also disclose use of JTV-5129 in addition to concentrations of JTV-519 that can be administered. The subject application therefore provides support for the amendments made to claim 6 and 18, as well as the newly added claims that address JTV-519, concentration ranges, and administration routes.

Thus, the subject application provides support for the amendments made to claims 1, 4, 6, 13,16, and 18, as well as the newly added claims 25-42. Applicant requests that the examiner enter the amendments presented herein.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 4, 5, 16, and 17 have been rejected as allegedly not enabled by the specification under 35 U.S.C. § 112, first paragraph. Claims 4, 5, 16, and 17 have also been rejected under 35 U.S.C. § 112, first paragraph (written description requirement). The Examiner stated "the specification fails to provide adequate written description for the genus recited in the methods and does not reasonably provide enablement for such a method of

employing a genus of agents that inhibits dissociation of a FKBP12.6 from RyR2 receptor" (12/29/05 Office Action, p. 3).

Applicants respectfully traverse these rejections and submit that in view of the amendments presented herein, the claims are fully described by the subject application and are fully enabled so that one of ordinary skill in the art could carry out the methods claimed without undue experimentation. The pending claims are directed to methods for treating or inhibiting atrial tachyarrhythmia in a human subject with an agent, wherein the agent is a derivative of 1,4-benzothiazepine. In Kaneko (Drug Development and Research, 1994; pages 430 and 435), which is incorporated by reference according to paragraph 3 on page 1 of the specification of the application, the structure of a derivative of 1,4-benzothiazepine is provided in addition to the statement that "various Ca^{2+} channel antagonists exist, and these compounds can be chemically classified: phenylalkylamines [Fleckenstein et al., 1969], dihydropyridines [Vater et al., 1972], diphenylalkylamines [Godfraind and Kaba, 1969], and benzothiazepines [Nagao et al., 1977]." Support for these amendments may further be found in the specification, on page 24, paragraphs 253-256. Accordingly, the pending claims have full written description support in the application, and no new matter has been added. Applicants point out that assaying the effect of JTV-519, a derivative of 1,4-benzothiazepine, on binding of FKBP12.6 to PKA-phosphorylated RyR2 is disclosed as Experimental Set III. As such, in view of the amendments to claims 4, 5, 16, and 17 and the above remarks, applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Rejections Under 35 U.S.C. § 102(b)

Claims 1-6 and 13-18 were rejected under 35 U.S.C. § 102(b) as anticipated by Nakaya *et al.*, *British Journal of Pharmacology*, 131:1363-1372 (2000) as evidenced by Yano *et al.*, *Circulation*, 107:477-484 (2003). Specifically, the examiner stated: "Nakaya *et al.* teach that JTV-519, which is known in the art to inhibit PKA phosphorylation of RyR2 receptor and dissociation of FKBP12.6 from the RyR2 receptor, exerts antiarrhythmic effects against atrial fibrillation and may be useful for the treatment of patients with atrial fibrillation" (12/29/05 Office Action, p. 5).

Applicants respectfully traverse these rejections and submit that in view of the amended claims, the Nakaya *et al.* and Yano *et al.* references do not anticipate the claimed invention, since work presented in these studies utilized non-human cardiac tissue. Neither Nakaya et al., nor Yano et al. disclose a method for inhibiting the onset of atrial tachyarrhythmias in a human subject by administering to the human subject an agent which restores normal gating to a type 2 ryanodine receptor (RyR2) channel in the human subject's heart, wherein the agent is a derivative of 1,4-benzothiazepine, or a method for inhibiting the onset of atrial tachyarrhythmias in a human subject by administering to the human subject an agent which enables FKBP12.6 to bind to PKA-phosphorylated type 2 ryanodine receptor (RyR2) channels in the human subject's heart, wherein the agent is a derivative of 1,4-benzothiazepine. Accordingly, in view of the forgoing remarks, applicants respectfully request that the examiner withdraw the rejection under 35 U.S.C. §102(b).

CONCLUSION

In view of the foregoing amendments and remarks, applicants believe that they have fully addressed the Examiner's concerns. Applicants respectfully request that the Examiner withdraw the current grounds of rejection and allow the claims to issue. The Examiner is invited to contact the undersigned with any questions.

The commissioner is authorized to charge any necessary fees in connection with this Amendment that might be due to Deposit Account No. 08-0219.

Respectfully submitted,

Date: 4/28/06

Jane M. Love, Ph.D.
Registration No. 42,812

Wilmer Cutler Pickering Hale and Dorr LLP
399 Park Avenue
New York, NY 10022
Tel. 212-937-7233 (direct)
Fax. 212-230-8888
Jane.Love@wilmerhale.com